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EXAMINER: HOTZELL, P

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DATE MAILED: 09/30/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 3-22-96.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire Three month(s), ~~or thirty days,~~ ~~whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-3, 5, 7, 8 and 14-21 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-3, 5, 7, 8 and 14-21 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

★ U.S. GPO: 1996-409-290/40029

15. Claims 1-3, 5, 7, 8, 14, 15 and 17-21 are pending and have been amended as requested by applicant in the response filed 3-22-96.

Claims 4, 6, 9-13 and 16 are canceled.

16. Claims 1-3, 5, 7, 8 and 20 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U.S. Patent No. 5,202,253.

17. Claims 14-21 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U.S. Patent No. 5,202,253 in view of Morrison or Queen.

Applicant's arguments have been considered but are not persuasive. The claims define an antibody by reciting the sequences of its having and light chain variable regions. The instant specification teaches that SEQ ID Nos 9 and 10, respectively are the nucleic acid and amino acid sequences of the heavy chain variable region of MAb HPC-4. Sequence ID Nos 11 and 12 are the nucleic and amino acid sequences of the light chain variable region of MAb HPC-4. The copending claims drawn to the HPC-4 antibody and hybridoma make obvious the instant claims which are drawn to antibodies having the identical sequences. The HPC-4 monoclonal antibody produced by the HB9892 hybridoma makes obvious the concept of antibodies which have the identical amino acid sequences. Those sequences are the

essential properties of the patented HPC-4 antibody which impart its defining functional properties.

18. Claims 1, 2, 5, 7 and 8 remain rejected under 35 U.S.C. § 102(b) and (e) as being anticipated by U.S. Pat. No. 5,202,253 or 5,147,638.

Applicant's arguments have been fully considered but are not found to be persuasive. The limitation in the claims specifying that the claimed antibody is not produced by hybridoma cell line HB9892 does not impart any structural differences to the claims which serve to distinguish over the cited references. The recited sequences are those which characterize the HPC-4 antibody produced by the HB9892 antibody. Recombinant HPC-4 antibodies produced by other cell lines transfected with vectors containing genes encoding the HPC-4 antibody have no apparent structural difference from antibodies secreted by the HB9892 hybridoma.

19. Claims 1-3, 5, 7, 8, 14-15 and 17-21 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Pat. No. 5,202,253 or U.S. Pat. No. 5,147,638 in view of Morrison or Queen applicant's arguments have been fully considered but are not persuasive.

To the extent that new claims 20 and 21 read on fusion proteins which are mouse/human chimeric antibodies or recombinant isotype switch variants of the HPC-4 monoclonal antibody, the

claims are obvious for reasons set forth in the previous office action.

Applicant argues that prior to actually cloning the genes, it was not possible to predict the isolated nucleotide sequences encoding the HPC-4 antibody or whether it would be expressed in functional form. Applicant concedes that one would have been motivated to produce the claimed invention but that a reasonable expectation of success was lacking since it was not predictable that one could clone the genes and express a recombinant antibody. Applicant asserts that no art has been cited showing that it was routine to clone antibodies.

Applicant's arguments have been fully considered but are not found to be persuasive. The '253 patent teaches in col.11, beginning at line 33, that HPC-4 cDNA can be cloned and sequenced using methods known to those skilled in the art. Methods for cloning and screening are described.

The Queen and Morrison and references applied in the instant rejection further establish that Ig gene cloning methods were known and had been successfully applied to clone a wide variety of different Ig genes. For example, Queen teaches that methods for antibody gene cloning and expression were well known, citing Reichmann et al., Nature 332, page 18, line 24. Reichmann et al. is also cited in applicant's specification (p15, lines 4-5) to establish the state of the prior art with respect to cloning of

immunoglobulin genes and is cited in the IDS filed 5/19/95. Reichmann et al. teaches a generally applicable strategy for cloning cDNAs encoding antibodies using primers derived from heavy and light chain constant regions (page 324, legend Fig. 1 Methods). Reichmann is illustrative of the state of the prior art at the time of applicant's invention and demonstrates that those of skill in the art recognized that cloning of immunoglobulin genes does not require specific knowledge of the sequence of the heavy and light chain variable regions. Because the J regions and constant regions of antibody heavy and light chains of differing specificities are highly conserved in their sequences, probes and primers derived from constant and J region sequences can be broadly applied to clone the genes encoding structurally diverse antibodies. It is noted that the strategy described by applicant on pages 9-10 for cloning the HPC-4 heavy and light chain variable regions, i.e. cDNA cloning, probing with CH and Ck probes, is the same general strategy described by Reichmann et al.

Thus, the cited prior art provides detailed guidance as to Ig cloning methods. The cited art establishes and applicant's specification admits, that methods for antibody gene cloning and expression were well known. The strategies used by applicant to clone and express the HPC-4 antibody heavy and light chains are the same as those which are described in the cited prior art and

which are admitted in the specification to have been known at the time of applicant's invention. The availability of the HPC-4 hybridoma, as provided by the deposit of the hybridoma in the '253 hybridoma, together with generally applicable antibody cloning methods which were known in the art at the time of applicant's invention would have provided one of skill in the art with a reasonable expectation of success in obtaining recombinant HPC-4 antibodies.

20. The specification is objected to under 35 USC § 112, first paragraph as the specification as originally filed does not provide support for the invention as is now claimed.

The specification provides no support for the concept of an antibody which bind to first and second epitopes.

No support is found for the limitation in the claims which excludes the HPC-4 monoclonal antibody produced by the ATCC HB 9892 cell line.

Claims 1-3, 5, 7, 8, 14, 15, and 17-21 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

21. The specification is objected to under 35 USC § 112, first paragraph as failing to enable one of skill in the art to practice the invention as claimed.

The specification does not adequately teach how to produce an antibody as claimed, which binds to two different epitopes, one which is in the activation peptide region of the Protein C heavy chain and a second which consists of calcium ions. It is conventional knowledge that a given monoclonal antibody is characterized by a single unique epitope binding specificity. The specification does not teach how to produce an antibody having the sequence claimed, which binds two distinct epitopes. One would not known how to produce such an antibody absent direction or guidance in the specification.

The claims require that the claimed antibody be comprised of only one member selected form the group consisting of the HPC-4 heavy and light chain polypeptides. The specification does not teach one of skill how to produce an antibody which has the properties of the HPC-4 antibody having only one member selected from the group consisting of the HPC-4 heavy chain and the HPC-4 light chain. The unique epitope binding site of antibodies in general and the HPC-4 antibody in particular, is formed by the association of properly folded heavy and light chain variable regions. The ability of each of the individual heavy or light chain variable region polypeptides to bind the HPC-4 epitope is improbable, and unpredictable and has not been demonstrated by evidence on this record. The ability of either of the HPC-4 heavy or light chain variable region polypeptides to pair with

other irrelevant heavy and light chain variable region polypeptides and to form a functional epitope binding molecule is also unpredictable. No direction or guidance are provided which would assist one of skill in the art in producing antibodies as claimed. No working examples are provided of antibodies as claimed which would provide guidance to one skilled in the art in producing the broadly claimed antibodies. As pointed out by applicant in the response, the response, the evidence of record in the '253 patent establishes unsuccessful attempts on the part of experts in the filed of anti-protein C antibodies to obtain similar anti-protein C and calcium binding antibodies. Thus, it is unpredictable that antibodies having only one or the other of the HPC-4 heavy and light chain variable regions could be obtained. The identities of heavy or light chain variable regions other than those of the HPC-4 antibody which could be paired with those of the HPC-4 antibody are unknown.

The specification does not teach how to produce antibodies as defined by claims 3 and 17, which contain human amino acid sequence other than the sequence defining the epitope binding specificity. No direction or guidance are provides as to those specific sequences of the HPC-4 heavy and light chain variable region which define the epitope binding specificity. Given the apparently complex nature of the epitope recognized by the HPC-4 antibody, it is unpredictable whether the precise residues

required for epitope binding could be identified without undue experimentation.

Undue experimentation would be required to produce the claimed antibody with a reasonable expectation of success.

Claims 1-3, 5, 7, 8, 14, 15 and 17-21 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

22. Claims 1-3, 5, 7, 8, 14, 15 and 17-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in reciting an antibody defined as having a sequence which is that of MAB HPC-4 where in the antibody is not the HPC-4 antibody deposited with the ATCC as ATCC NO. HB 9892. It is not known what is meant by HPC-4. The manner in which the claimed antibody is intended to differ from that produced by the hybridoma deposited as HB 9892 is unclear. It is further unclear how a recombinant antibody which is not the HPC-4 antibody deposited with the ATCC as ATCC NO. HB 9892 (e.g. as recited in claim 1) differs from a recombinant HPC-4 as deposited with the ATCC as ATCC No. HB 9892 (e.g. as recited in claim 20). Does the claimed antibody have the entire mouse variable and constant region of the HPC-4 antibody, the identical variable region of the mouse antibody and optionally a different

constant region or no constant region? The metes and bounds of the claims are unknown.

It is also pointed out that the HPC-4 hybridoma, not the antibody, which has been deposited. The accession number recited in claims 20 and 21 is incomplete, in lacking the prefix "HB".

Claim 20 is indefinite in reciting a "fusion" protein. The meaning is not known.

Claim 21 is indefinite in reciting a "different protein". The nature of the difference is not known.

Claims 1, 3, 5, 7, 14-16 and 17-19 are indefinite in the recitation of "degenerate sequences thereof". The meaning is not known.

Claims 3 and 17 are indefinite in the recitation of an antibody containing a human amino acid sequence "other than the sequence defining the epitope binding specificity". The sequence referred to is not known.

23. Claims 20 and 21 are rejected under 35 U.S.C. § 103 as being unpatentable over US Pat No. 5,202,253, US Pat 514,638, Morrison and Queen as applied to claims 1-3,5,7,8 and 14-19 above, and further in view of US Pat No. 5,298,599.

The '599 patent teaches producing fusion proteins to facilitate purification. It would have been obvious to clone the genes encoding the HPC-4 antibody in view of the combined teachings of US Pat No. 5,202,253, US Pat 514,638, Morrison and

Queen for reasons previously discussed. Having obtained the nucleic acids encoding the HPC-4 antibody, it would have been obvious to use methods as taught by the '599 patent to produce constructs encoding fusion proteins of the HPC-4 Protein. One would have been motivated to do so in order to obtain the advantages discussed in the '599 patent.

Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Paula Hutzell, Ph.D, whose telephone number is (703) 308-4310. The Examiner can normally be reached on Monday-Thursday from 9:00 AM- 6:00 PM. The Examiner can also be reached on alternate Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Marian Knode, can be reached on (703)-308-4311. The fax phone number for this Group is (703)-308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

PAULA K. HUTZELL
PRIMARY EXAMINER
GROUP 1800

Hutzell/sg
September 29, 1996